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Treatment of Severe Chronic Urticaria: a Retrospective Single Center Analysis of Patients Treated from 2009 - 2016

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Abstract

Chronic urticaria is defined as daily or intermittent appearance of hives for more than 6 weeks. Patients with more severe forms of the disease have increased needs for immune modifying agents for disease control, and among these cyclosporine is the mainstay of treatment. Material and Methods: This retrospective study included patients treated for chronic urticaria from 2009 – 2016 at the Department of Dermatology of the Military Medical Academy. Results: There were 145 treated patients, of whom 20 (13.8%) were resistant to at least two lines of treatment (maximum dose of antihistamine monotherapy, combination of antihistamines, addition of dapsone and short courses of corticosteroids). The patients were treated with cyclosporine (6 males and 14 females; average age 40.05 years). Median duration of treatment was 6 months (range: 2 - 17). In 9 (45%) patients, cyclosporine treatment led to a complete response, in 3 (15%) occasional urticarial plaques developed in spite of treatment, while in 2 (10%) urticaria was resistant to cyclosporine treatment, with continuous disease activity. During the follow-up period, 20% of patients experienced adverse effects. Conclusion: In conclusion, 13.8% of patients were resistant to first-line standard treatment. In these patients, cyclosporine can be regarded as a safe and effective treatment modality, with relatively short course of treatment, but 10% of patients can be regarded as treatment resistant and around 20% experience adverse effects, pointing to the need for further treatment options, including omalizumab.

Key words

Urticaria; Chronic Disease; Cyclosporine; Immunosuppressive Agents; Retrospective Studies

Chronic urticaria (CU) is defined as daily or intermittent appearance of hives for more than 6 weeks. The severe forms may be a therapeutic challenge to the treating physician and frustrating for the patients. Single episodes of hives typically last less than 24 hours, and symptoms are often worse at night. Approximately one half of chronic urticaria patients experience coexistent angioedema (1).

The etiology and pathogenesis of CU are complex, and include cases with associated autoimmune disorders like Hashimoto's thyroiditis, chronic infections like Helicobacter pylori, and cases aggravated by non-steroidal anti-inflammatory drugs and other histamine-releasing agents (2 - 4). In almost 70% of patients with CU, in spite of extensive investigations, the cause of this condition remains unknown - chronic idiopathic urticaria (CIU). About 30 - 50% of patients with CIU have circulating histamine releasing autoantibodies to the high-affinity IgE receptor FcεRI on basophils and mast cells or, less commonly, antibodies to IgE. The term autoimmune urticaria is widely accepted for this subgroup of patients (5). The autologous serum skin test (ASST) is currently one of the most useful tests for suspected diagnosis of chronic autoimmune urticaria (CAU) (sensitivity: 65 – 81%; specificity: 71 – 78%), but confirmatory in vitro test is also necessary (6).

The mainstay of initial treatment for CU is the

use of antihistamines (up to the maximum dose). Addition of leukotriene antagonists, dapsone and other agents (sulfasalazine, and colchicine) is regarded as second-line treatment according to the existing guidelines. In resistant cases, cyclosporine is the first-line treatment for chronic urticaria. Omalizumab, a humanized recombinant IgG1 kappa monoclonal anti-IgE antibody, previously approved for treatment of moderate to severe persistent asthma since 2003, was approved for the treatment of CU unresponsive to H1 antihistamines in 2014.

Material and Methods

This retrospective study included patients with CU treated from 2009 – 2016 at the Department of Dermatology, Military Medical Academy (MMA). The hospital database was used to retrieve patients' medical records. Patients who were resistant to at least two lines of treatment (maximum dose of antihistamine monotherapy, combination of antihistamines, addition of dapsone and short courses of corticosteroids) were treated with cyclosporine. Laboratory tests were done before treatment, 7 days later and/or prior to discharge. Early therapeutic efficacy was evaluated 3 weeks after hospitalization, based on reduced number of urticarial plaque, and the number of single episodes. The data on the disease characteristics (i.e. age of onset, angioedema, autologous skin test results, associated diseases) were analyzed. Duration of treatment, treatment efficacy and adverse effects were recorded during the follow-up period. Descriptive statistics were used to describe the basic features of the study data.

Results

A total of 145 patients with CU were treated at the Department of Dermatology, MMA, Belgrade from January 1, 2009 to January 1, 2016. Twenty patients (13.8 %) with severe form of CU were resistant to at least two lines of treatment (Table 1). There were 14 (70%) females and 6 (30%) males. The average age of patients was 40.05 (range: 18 - 77 years).

In treatment-resistant cases, early onset urticaria (under the age of 18 years) was found in 3 patients (15%), 12 patients (60%) had adult-onset urticaria (18 to 50 years), and 5 patients (25%) were older than 50 years at the onset of the disease. The majority of patients had angioedema (17 patients, 85%). The autologous serum skin test (ASST) was performed in all patients. It was positive in 13 patients (65%), and negative in 7 (35%). An associated thyroid disorder was documented in 2 patients (10%). Helicobacter pylori infection was diagnosed in 3 (15%) patients, and eradication treatment with antibiotics was recommended. In the majority of patients (12.60%) CRP was elevated, with average value of 17.3.

All 20 patients were previously treated with a short course of corticosteroids, 18 patients (90%) received different combinations of systemic antihistamines and 7 patients (35%) received dapsone combined with

Table 1. Treatment patterns of chronic urticaria at the Department of Dermatology, MMA from 2009 - 2016

Medications	Number of patients	Treatment efficacy (%)*
Antihistamines	143	64.34%
Antihistamines + short course of corticosteroids	46	39.13 %
Dapsone	12	41.67%
Cyclosporine	20	60%

*% of patients with disease control

Table 2. Treatment of chronic urticaria with cyclosporine

Initial dose	3 - 5 mg/kg/day	
Average dose	4.4 ± 0.74 mg/kg/day	
Duration of treatment	2 - 17 months, median - 6 months	
Response	Complete	9 patients (45%)
	Partial	3 patients (15%)
	Without effects	2 patients (10%)
	Lost to follow up	6 patients (30%)
Adverse effects	Hypertension	1 patient (5%)
	Elevated urea and creatinine	2 patients (10%)
	Leukopenia	1 patient (5%)

antihistamines, with unsatisfactory therapeutic results (Table 2). The initial dose of cyclosporine was 3 mg/kg/day in 3 patients, 4 mg/kg/day in 6 patients and 5 mg/kg/day in 11 patients, with the average dose of 4.4 ± 0.74 mg/kg/day. Median duration of cyclosporine treatment was 6 months (range: 2 - 17). In 9 (45%) patients, cyclosporine treatment led to complete response, in 3 (15%) occasional urticarial plaques developed despite the treatment, while in 2 (10%) urticaria was resistant to cyclosporine treatment, with continuous disease activity. During the follow-up period, hypertension was found in one patient (5%), elevated creatinine levels were found in two patients (10%) elevated urea levels in one (5%) and leukopenia in another patient (5%).

In total, of 145 patients, 20 patients (13.8%) were resistant to standard antihistamine treatment (at maximum doses and in combination). Of patients treated with cyclosporine, 2 patients (10%) were resistant to treatment and 4 patients (20%) experienced adverse effects to cyclosporine. It is estimated that 30% of CU patients are in need for other treatment options, including omalizumab, which is recommended by current treatment guidelines.

Discussion

Chronic urticaria is defined as the daily or almost daily occurrence of hives for more than 6 weeks. This condition is more common in adults, and affects women more frequently than men. In general, CU is classified as either CAU or CIU. In CAU, circulating immunoglobulin G (IgG) autoantibodies react to the alpha subunit of the high-affinity IgE receptor on dermal mast cells and basophils, leading to chronic stimulation of these cells and the release of histamine and other inflammatory mediators which cause urticaria and angioedema. CAU is also associated with antithyroid antibodies in approximately 27% of cases, as well as other autoimmune conditions such as vitiligo. It has also been proposed that Helicobacter pylori may play an indirect role in the etiology of CAU by reducing immune tolerance and inducing autoantibody formation (3 - 5).

Histamine is the main mediator of urticaria, and antihistamines represent the mainstay of initial treatment of CU. Various studies on the role of antihistamines in CU showed a 44 to 90% response rate (8). Antihistamine efficacy is often patient specific and, therefore, more than one antihistamine should be tried before assuming therapeutic failure with these agents. In patients who do not achieve adequate disease control at standard doses, it is common practice to increase the antihistamine dose beyond the usual recommended dose (9). Current European Academy of Allergy and Clinical Immunology (EAACI) guidelines recommend up to four times the usual recommended dose of antihistamine in patients whose symptoms persist with standard therapy (10). In our case series, antihistamine therapy induced disease control in 64.34% of inpatients.

In some patients with severe urticaria, who are inadequately responsive to antihistamines, a brief course of oral corticosteroids is recommended. Long-term corticosteroid therapy should be avoided, because of the side effects associated with prolonged use of corticosteroids (10, 11). According to the United States Joint Task Force practice parameters guidelines, if dose escalation of sedating H1 antihistamines or addition of a combination antihistamine (doxepin) is ineffective or not tolerated due to excessive sedation, therapy options include anti-inflammatory medications (hydroxychloroquine, dapsone, sulfasalazine, colchicine), immunosuppressants (cyclosporine, mycophenolate, tacrolimus, methotrexate) or biologics, notably omalizumab (11). In our study, addition of a short-course corticosteroids to antihistamine treatment was effective in 29.1%, while addition of dapsone induced disease control in 41.7% of treated patients.

The best studied immunosuppressive therapy for CU is cyclosporine. Cyclosporine is the mainstay of treatment for severe forms of chronic urticaria. The main mechanism of action of cyclosporine consists in inhibition of HT-cell function. In stimulated T-cells, cyclosporine inhibits activation by suppressing IL-2 production and expression. This inhibition blocks the activation of T-helper cells, T-regulatory cells, natural killer cells and monocytes. The inhibition seems to be dose-dependent and also affects other calcium-dependent events, such as nitric oxide activation, cell degranulation and apoptosis. In stimulated mast cells, cyclosporine decreases histamine release and there is decreased production of chemotactic factors and down-regulation of various cell adhesion molecules (12).

Cyclosporine was evaluated in the treatment of CU in 11 clinical trials based on PubMed search, including 4 randomized controlled trials. There are 2 randomized-controlled trials that demonstrated significant improvement with cyclosporine, compared to placebo in the treatment of CU, resulting in remission of hives in 26% of subjects (13, 14). One of these four studies compared clinical efficacy and safety of short- and long-term cyclosporine applications. The clinical improvement was dramatic in the first month of treatment in both groups. There was no significant difference in the frequency of responses, side effects and reduction of weal numbers and itch in either group. However, the study concluded that prolonged therapy, over 1 month, provides little benefit in the clinical improvement (15). Randomized controlled studies of cyclosporine in CU have been for periods of 4 to 16 weeks, with doses between 3 and 5 mg/kg (13 - 16). In our study, the treatment was longer, the median duration of treatment was 6 months (range: 2 -17 months) and the average initial dose of cyclosporine was 4.4 ± 0.74 mg/kg/day. In most of the studies where higher doses were administered, side effects such as hypertension, peripheral neuropathy and increased serum creatinine, were reported in 20 - 30% of patients. In most patients they were transient or improved following dose reduction. When low doses of cyclosporine were administered (2 – 3 mg/kg), most studies reported a very low incidence of side effects (13, 17, 18). In our study, treatment with cyclosporine was well tolerated by the majority of patients (16 patients, 80%). During the follow up period, hypertension was found in one patient, but it did not compromise the treatment. Increased urea and creatinine levels were found in 2 patients and leukopenia in another patient, which were the main reasons for treatment cessation in a total of 3 (15%) patients.

Cyclosporine represents a good therapeutic option for treatment of severe CU resistant to other treatment options. Its efficacy and risk/benefit ratio is well documented in randomized placebo controlled

trials and also uncontrolled trials. The European Academy of Allergology and Clinical Immunology guidelines for the definition, classification, diagnosis and management of urticaria, published in 2013, recommended cyclosporine along with omalizumab and montelucast as a third line therapy for CU. Omalizumab (anti-IgE) has now been shown to be dramatically effective in selected patients with chronic spontaneous urticaria, cholinergic urticaria, cold urticaria and solar urticaria. Larger double-blind placebo-controlled studies are needed to confirm these results. High cost of omalizumab treatment regimen, defines cyclosporine as the treatment of choice in patients with treatment resistant CU (10).

Conclusion

In conclusion, 20 of 145 patients (13.8%) with chronic urticaria treated in hospital settings presented with a severe form of the disease, with increased need for immune response modifying agents for disease control. Cyclosporine is the mainstay of treatment for severe forms of chronic urticaria and it can be regarded as safe and effective treatment modality in majority of patients with relatively short course of treatment. Of patients treated with cyclosporine, 10% could be regarded as treatment resistant, and around 20% experienced adverse effects leading to cessation of treatment, pointing to the need for further treatment options, including omalizumab.

Abbreviations

CU- chronic urticaria
CIU - chronic idiopathic urticaria
CAU - chronic autoimmune urticaria
MMA - Military Medical Academy
ASST - autologous serum skin test
IgE - immunoglobulin E
IL-2 - interleukin-2
EAACI - European Academy of Allergy and Clinical Immunology

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Lečenje teškog oblika hronične urtikarije – retrospektivna unicentrična studija pacijenata lečenih u periodu 2009–2016. godine

Sažetak

Uvod. Hronična urtikarija predstavlja svakodnevno ili gotovo svakodnevno prisustvo urtika na koži duže od šest nedelja. Pacijenti sa teškom formom hronične urtikarije, koja je rezistentna na terapiju maksimalnim dozama antihistaminika, uz upotrebu kortikosteroida, imaju veću potrebu za terapijom imunosupresivnim agensima, među kojima ciklosporin i dalje predstavlja terapiju prvog izbora. U ovom članku, mi smo analizirali efikasnost i bezbednost lečenja ciklosporinom kod pacijenata sa teškim oblikom hronične urtikarije, lečenih u Vojnomedicinskoj akademiji u Beogradu u periodu 2009–2016. godine.

Ispitanici i metode. Učinjena je retrospektivna analiza pacijenata sa teškim oblikom hronične urtikarije lečenih na Klinici za kožne i polne bolesti Vojnomedicinske akademije od 2009. do 2016. godine, a podaci su dobijeni iz bolničke baze podataka i medicinske dokumentacije. U navedenom periodu, ukupno 145 pacijenata lečeno je od hronične urtikarije u bolničkim uslovima, od kojih njih 20 (13,8%) sa teškim rezistentnim oblikom hronične urtikarije koja je zahtevala lečenje ciklosporinom. Laboratorijske analize su uzete pre tretmana, posle sedam dana i/ili na kraju hospitalizacije. Rana terapijska efikasnost je ocenjena nakon tri nedelje po otpustu, na osnovu redukcije broja urtika na koži, kao i njihove učestalosti. Trajanje terapije, neželjeni efekti tokom terapije, efikasnost lečenja i razlog za prekid lečenja praćeni su na kontrolnim pregledima pacijenata.

Rezultati. Ukupno je lečeno 20 pacijenata, 14 žena i 6 muškaraca, prosečne starosti 40,5 godina. Prethodni modaliteti lečenja bili su kratki kursevi kortikosteroida kod svih 20 pacijenata (100%), antihistaminici u maksimalnim dozama, kao i kombinacije više različitih antihistaminika kod 18 pacijenata (90%) i dapson kod sedam pacijenata (35%). Prosečna doza ciklosporina bila je 4,4 ± 0,7 mg/kg. Medijana trajanja terapije ciklosporinom bila je šest meseci (2–17). Kod devet pacijenata (45%), terapija ciklosporinom dovela je do potpunog terapijskog odgovora, tri pacijenta (15%), imala su parcijalan terapijski odgovor sa povremeno prisutnim urtikama na koži, u manjem broju i sa manjom učestalošću, dok kod dva pacijenta (10%) nije bilo terapijskog efekta. Tokom perioda praćenja, kod četiri pacijenta (20%) registrovana su neželjena dejstva terapije. Hipertenzija je zabeležena kod jednog pacijenta (5%), povišene vrednosti uree i kreatinina kod dva pacijenta (10%) i leukopenija kod jednog pacijenta (5%).

Zaključak. U našoj studiji 13,8% pacijenata je rezistentno na standardnu terapiju koja se koristi u lečenju hronične urtikarije. Kod većine ovih pacijenata, ciklosporin predstavlja bezbednu i efikasnu terapijsku opciju sa relativno kratkim vremenom trajanja terapije. Rezistentnost na terapiju ciklosporinom zabeležena je kod 10% pacijenata, dok se kod 20% registruju neželjeni efekti, zbog čega kod ovih pacijenata postoji potreba za drugim terapijskim opcijama, uključujući i omalizumab.

Ključne reči

Urtikarija; Hronična bolest; Ciklosporin; Imunosupresivni lekovi; Retrospektivne studije